

Spinal Muscular Atrophy

Molecular pathogenesis, neurogenic morphology, clinical variation, and
mechanism-based therapy

Pathology teaching lecture

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Learning outcomes

- Identify the specific neuronal population affected in 5q-associated SMA.
- Explain how SMN1 loss and SMN2 splicing interact to alter SMN protein availability.
- Interpret neurogenic muscle morphology using denervation and compensatory reinnervation.
- Distinguish textbook-described clinical phenotypes and molecular therapeutic strategies.

SMA is a disorder of lower motor neuron survival

- A group of genetically related childhood disorders, rather than a primary myofiber degeneration.
- Marked lower motor neuron loss produces progressive muscle weakness and atrophy.
- The most common forms involve the chromosome 5q SMN gene system.
- The extent and timing of neuron loss shape the clinical phenotype.

Where does the primary lesion occur?

Neural compartment

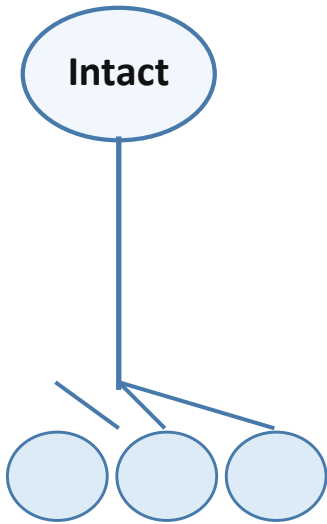
- Lower motor neurons are the primary degenerating cells.
- Reduced innervation deprives skeletal myofibers of normal neural input.
- Residual neurons may innervate surviving muscle fibers.

Muscle compartment

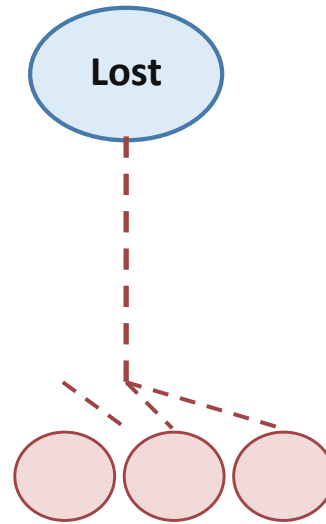
- Atrophy is a downstream consequence of lost motor neuron input.
- Compensatory fiber hypertrophy can coexist with extensive atrophy.
- Muscle morphology therefore records a neurogenic process.

Motor units connect neuronal loss to muscle atrophy

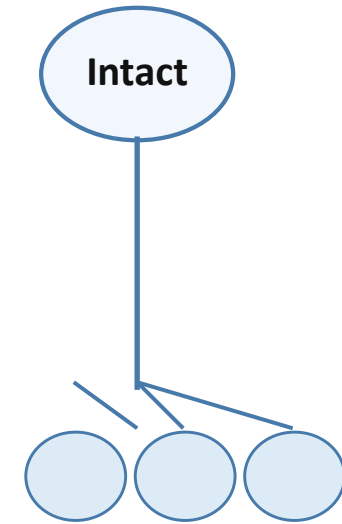
A motor unit comprises one motor neuron, its axon, and the myofibers it innervates.



Remaining units retain innervation

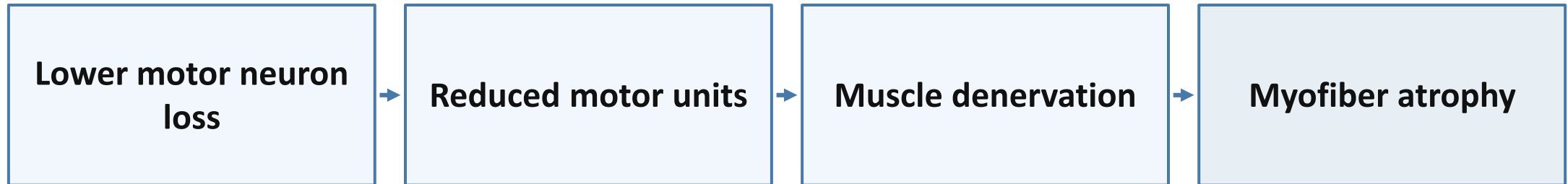


Lost unit → denervation → atrophy



Schematic; Not anatomical scale.

Motor neuron depletion produces a cascade of tissue effects



The sequence accounts for weakness without requiring primary degeneration of the myofiber itself.

Schematic causal model based on Robbins Chapters 27–28.

Why the term “spinal muscular atrophy” can mislead

- “Muscular atrophy” describes the downstream muscle phenotype.
- For 5q-SMA, the primary disease target is the lower motor neuron.
- A muscle biopsy may reveal denervation, not a primary structural myopathy.
- The genetic defect is upstream of both neuronal loss and myofiber atrophy.

Genetic architecture of the common 5q forms

- The common disease-associated locus lies on chromosome 5q.
- SMN1 normally provides most of the functional SMN protein.
- The adjacent SMN2 gene has similar sequence but different transcript processing.
- Clinical variability reflects, in important part, how much residual SMN can be produced.

5q-SMA is inherited in an autosomal recessive pattern

- 5q-SMA as an autosomal recessive SMN1 loss-of-function disorder.
- A disease genotype results when both relevant SMN1 alleles fail to provide adequate function.
- Heterozygous carriers are a key family-counselling concept.
- Allelic segregation and clinical severity are distinct questions: SMN2 modifies phenotype.

Autosomal recessive SMA: Inheritance logic

Illustrative cross: Two heterozygous carrier parents

SMN1 / SMN1

Unaffected non-carrier

SMN1 / variant

Unaffected carrier

Variant / SMN1

Unaffected carrier

Variant / variant

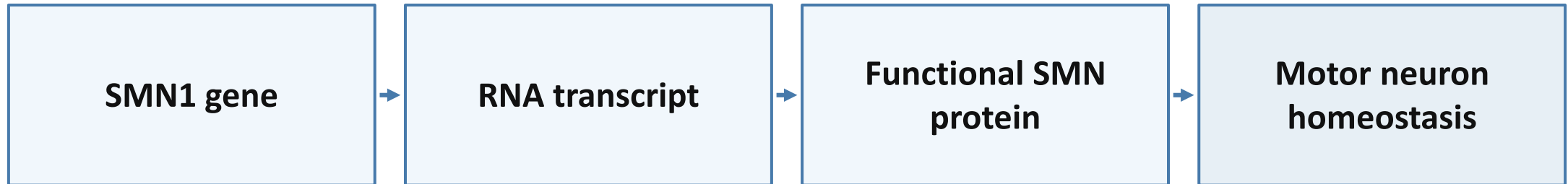
Affected genotype

Expected genotypic proportions: 1 : 2 : 1 for each pregnancy; Illustrative Mendelian model.

Robbins-reported incidence: Approximately 1 in 6000 births

- The chapter on skeletal muscle reports an incidence of 1 in 6000 births.
- This figure describes the textbook source, not a country-specific surveillance estimate.
- Population incidence does not determine the severity of an individual affected child.
- Avoid confusing disease incidence with carrier frequency or recurrence probability.

SMN1 is the main source of survival motor neuron protein



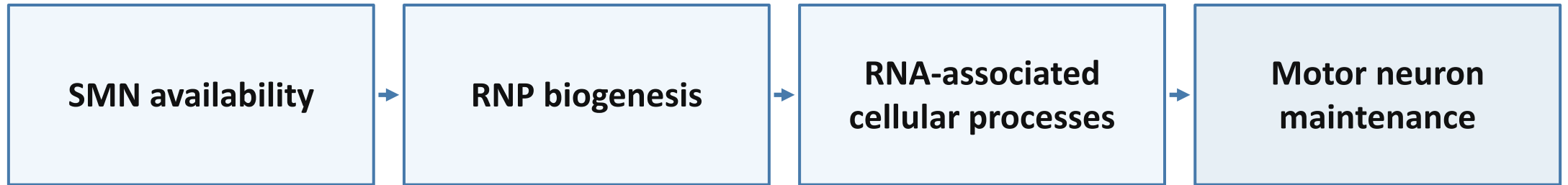
Loss-of-function variants in SMN1 diminish the dominant source of SMN protein.

SMN function to spliceosome assembly and ribonucleoprotein biogenesis.

The SMN protein participates in spliceosome assembly

- The spliceosome is the RNA-processing machinery relevant to removal of introns.
- SMN as participating in spliceosome assembly.
- Loss of SMN has consequences beyond a single downstream gene.
- This mechanistic role explains why an RNA-processing protein can be central to a neurogenic disorder.

SMN function extends into ribonucleoprotein biology



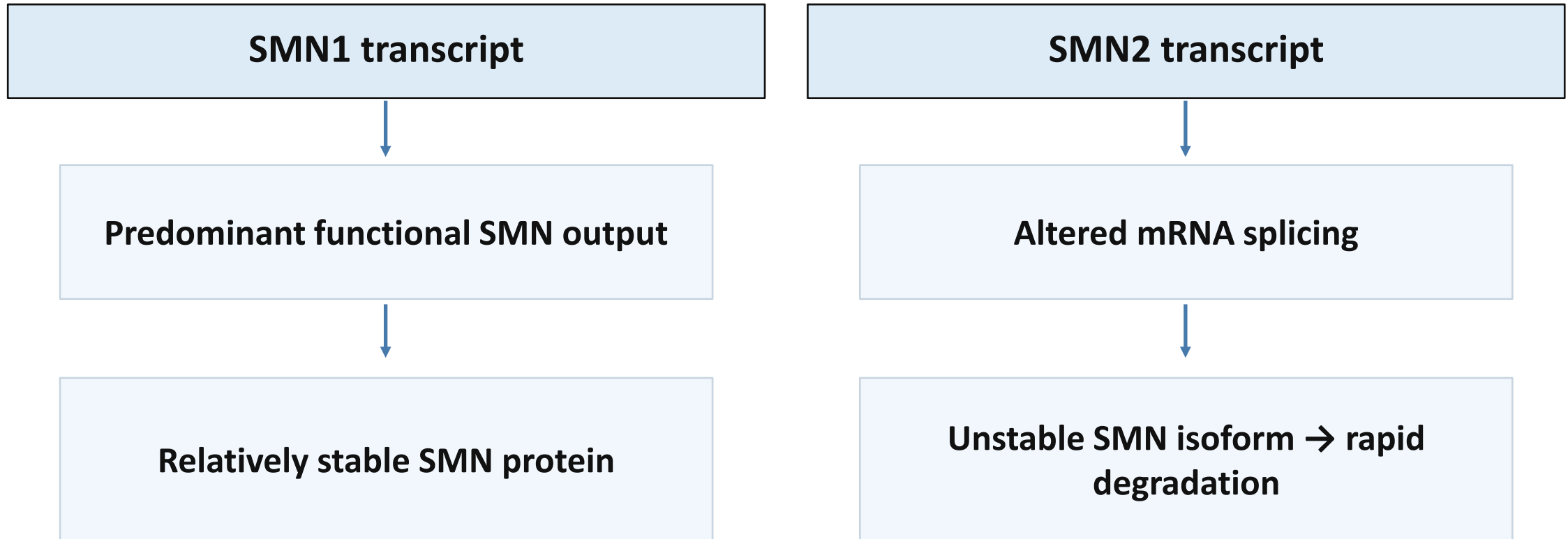
The source also links SMN1 to ribonucleoprotein biogenesis and neuronal homeostasis.

This diagram summarizes roles named in Chapter 27; It does not specify unreported downstream effectors.

Selective motor neuron vulnerability is a separate question

- SMN supports fundamental cellular RNA-associated machinery.
- The phenotype nevertheless prominently involves lower motor neurons.
- The supplied Robbins extract does not establish one complete molecular explanation for that selectivity.
- Do not invent a precise downstream death pathway when the source does not give one.

SMN1 and SMN2: Similar genes, different RNA outputs

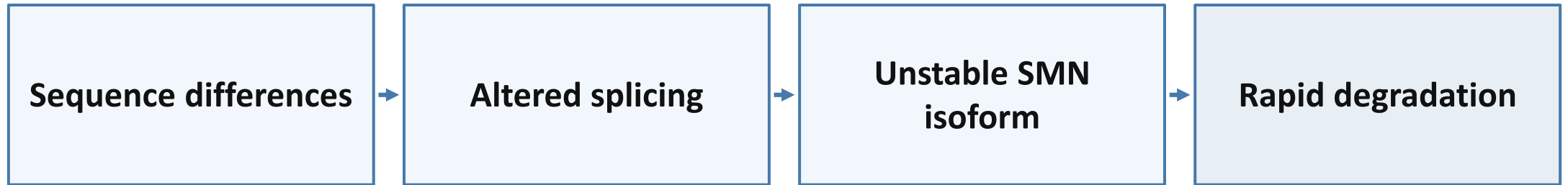


A few sequence differences change splicing; SMN2 only partly compensates for loss of SMN1.

SMN1 and SMN2 are adjacent but not interchangeable

- A few base-pair differences distinguish SMN2 from SMN1.
- Those differences alter SMN2 mRNA splicing.
- The altered SMN2 transcripts preferentially yield an unstable protein isoform.
- Thus gene similarity does not imply equal functional protein output.

SMN2 sequence differences shift the protein outcome



Compared with SMN1, SMN2 supplies less stable functional SMN protein per copy.

Why SMN2 cannot fully replace SMN1

SMN1 output

- Most SMN protein ordinarily derives from SMN1 transcripts.
- Functional protein supports critical RNA-processing functions.
- Loss of SMN1 removes the major source of SMN.

SMN2 output

- SMN2 transcripts have altered splicing due to sequence variation.
- A substantial output is an unstable isoform rapidly degraded.
- Residual output influences the disease phenotype.

SMN2 exhibits copy-number variation

- Robbins explicitly identifies SMN2 as a copy-number-variable gene.
- Even unaffected individuals may carry one or multiple copies per chromosome 5.
- The number of SMN2 copies varies independently of whether SMN1 is dysfunctional.
- Copy number is a biologic modifier, not the causal SMN1 lesion.

The modifier model: SMN1 lesion plus SMN2 dosage



Variation in SMN2 copy number helps explain differing phenotypes among people with 5q-SMA.

Qualitative relationship only; The Robbins excerpt supplies no exact copy-number classification.

SMN2 copy number is not itself a diagnosis

- The causal criterion within the supplied source is loss-of-function of SMN1.
- SMN2 is relevant because it modifies available SMN after SMN1 function is lost.
- A modifier must not be mistaken for an independent causative genotype.
- Exact SMN2 thresholds for clinical subtypes are not provided in the cited extract.

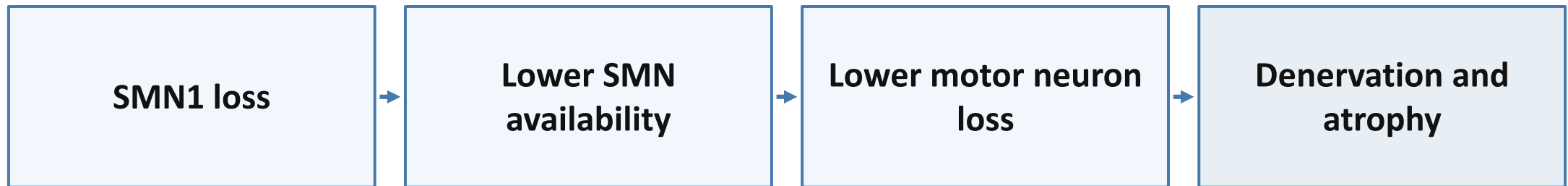
SMN1 loss-of-function is the unifying 5q lesion

- All 5q-SMA forms to loss-of-function mutations in SMN1.
- Deletion is described as the usual mutation class.
- Different clinical expressions do not require unrelated primary genes.
- Residual SMN biology helps connect a common lesion to a phenotypic spectrum.

Causal lesion and modifier: Do not conflate them

Feature	SMN1	SMN2
Principal role	Major functional SMN source	Alternative SMN source
Disease relation	Loss-of-function causes 5q-SMA	Copy number helps modify phenotype
Transcript behavior	Produces predominant SMN output	Splicing favors unstable isoform
Teaching point	Establish the upstream defect	Interpret variation in residual output

One integrated molecular model of 5q-SMA



SMN2 transcript output modifies the amount of residual functional protein upstream of neuron loss.

A genetic lesion can have prenatal morphologic consequences

- Motor neuron loss associated with SMN1 deficiency may begin in utero.
- Some muscle fibers may therefore never receive normal initial innervation.
- Others may lose innervation after the motor unit is initially established.
- Both mechanisms can converge on a similar pattern of severe myofiber atrophy.

Two routes to a denervated muscle fiber

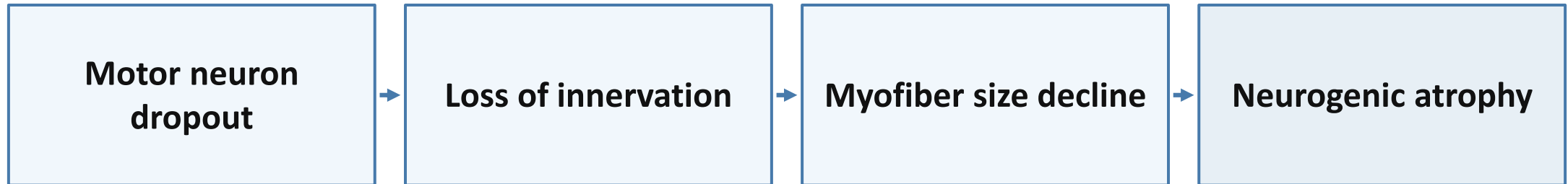
Failure of initial innervation

- Motor neurons may be lost early in development.
- A subset of developing fibers may lack appropriate innervation.
- The resulting fibers remain markedly small.

Loss of established innervation

- Previously innervated fibers lose their input.
- Denervation reduces trophic and functional support.
- Remaining motor neurons can partly compensate.

Denervation translates neuronal loss into muscle pathology

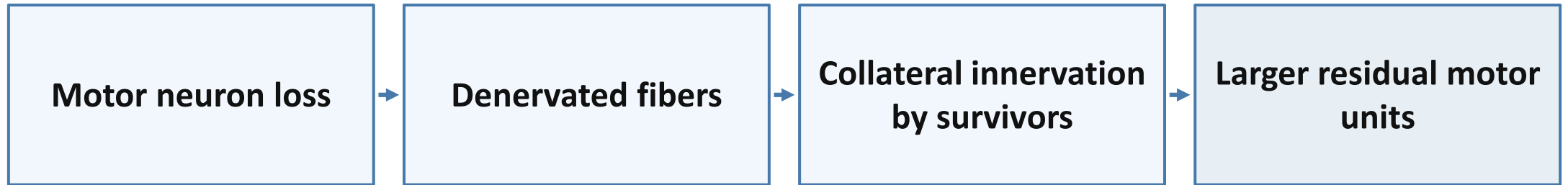


The sequence is a tissue-level consequence of neuronal loss rather than a primary myofiber metabolic defect.

The motor unit organizes muscle fiber phenotype

- Each muscle fiber belongs to a motor unit supplied by a particular motor neuron.
- Muscle fiber type reflects the identity of its innervating motor neuron.
- Loss and regrowth of innervation can therefore change the arrangement of fiber types.
- The motor-unit concept explains fiber-type grouping after reinnervation.

Reinnervation can enlarge surviving motor units



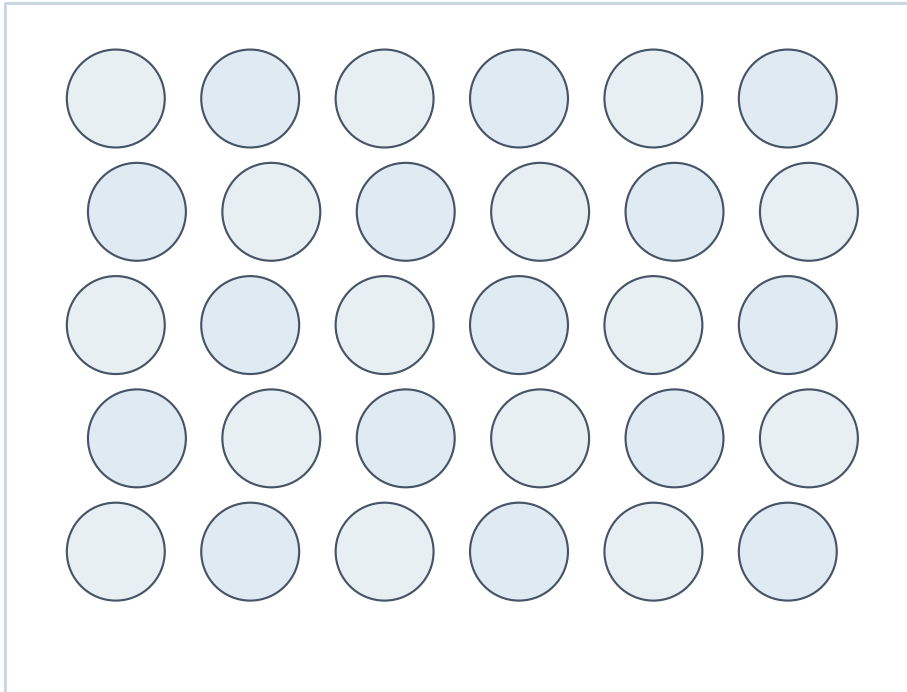
Surviving axons can capture fibers that formerly belonged to different motor units.

Compensatory hypertrophy is not primary fiber growth

- Normal or hypertrophied fibers amid extensive infantile SMA atrophy.
- These preserved large fibers receive innervation from surviving motor neurons.
- Their size contrasts with the numerous denervated atrophic fibers.
- The juxtaposition reflects unequal survival of motor-unit input.

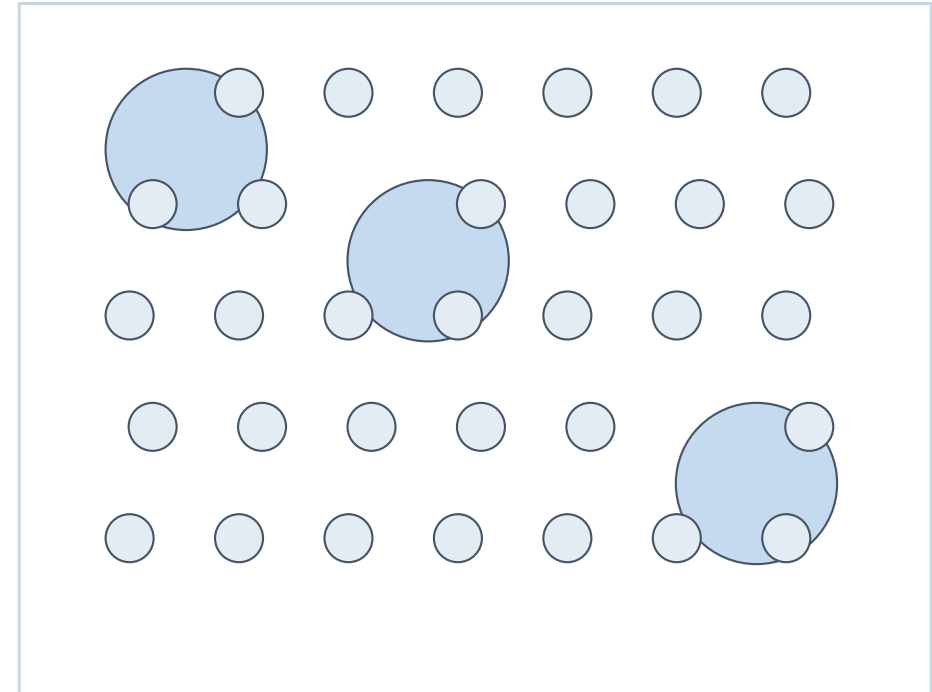
Severe infantile SMA: Rounded atrophy and surviving fibers

Schematic normal mosaic



Relatively uniform myofiber calibers

Schematic SMA pattern



Many small rounded fibers; Rare large survivors

Original conceptual schematic; Not histopathology or scale-preserving.

Severe infantile SMA has a distinctive muscle pattern

- Large zones of severely atrophic round myofibers are described.
- Scattered normal-caliber or hypertrophied fibers appear singly or in small groups.
- The larger fibers reflect retained or regained neuronal innervation.
- The finding is descriptive; The source excerpt does not make biopsy alone a molecular confirmation.

Infantile SMA morphology versus generic neurogenic change

Classic neurogenic atrophy

- Denervated fibers often become angular or flattened.
- Reinnervation may produce fiber-type grouping.
- Loss of an enlarged unit may generate grouped atrophy.

Severe infantile SMA

- Many severely small fibers may be rounded.
- Scattered normal or hypertrophied fibers remain.
- Loss of initial developmental innervation can contribute.

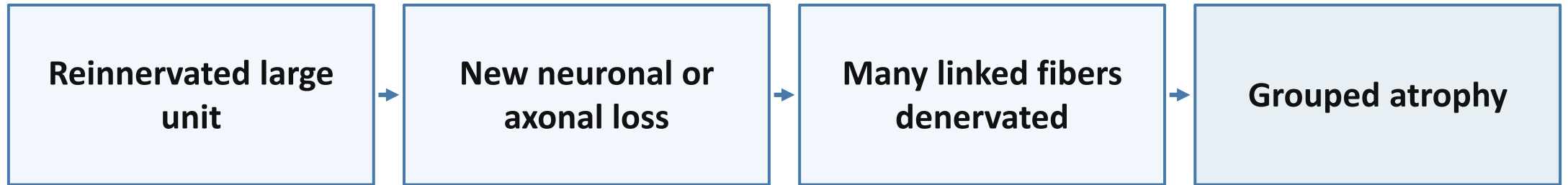
Why rounded atrophic fibers can occur in infantile SMA

- If initial innervation never becomes established, muscle-fiber development is affected early.
- The source explicitly describes very small rounded fibers in severe infantile SMA.
- This appearance differs from the classic angular profile often seen after denervation.
- Shape is a morphologic clue, not a stand-alone molecular mechanism or diagnosis.

Fiber-type grouping follows successful collateral reinnervation

- A surviving motor axon can innervate fibers that previously belonged to other units.
- Because the innervating neuron influences muscle-fiber type, neighboring fibers may become uniform in type.
- Reinnervation can generate larger-than-normal motor units.
- Fiber-type grouping therefore signals adaptation to prior denervation.

Grouped atrophy can follow subsequent unit failure



A compensatory enlargement of motor units can create clusters of fibers vulnerable to a later shared loss of input.

Neurogenic versus primary myopathic injury

Neurogenic mechanism

- Loss of neuron/axon disrupts neural support.
- Atrophy and reinnervation are central tissue processes.
- Grouping phenomena relate to motor unit reorganization.

Primary myopathic mechanism

- Direct myofiber injury may cause segmental degeneration.
- Myophagocytosis and regeneration follow necrosis.
- Damage can release muscle enzymes such as creatine kinase.

Reading a hypothetical muscle specimen

Finding	Mechanistic interpretation	Important limitation
Small rounded fibers with rare large fibers	Infantile SMA-type denervation pattern	Not molecular confirmation
Angular atrophic fibers	Denervation of established motor units	Not specific for SMA
Fiber-type grouping	Collateral reinnervation	Requires appropriate fiber typing
Segmental fiber necrosis	Primary myofiber injury mechanism	Supports another process

A morphology-first diagnostic argument has limits

- Neurogenic muscle changes support denervation but do not uniquely identify its cause.
- Motor neuron disorders, radiculopathy, and neuropathy can also produce neurogenic atrophy.
- The distinctive infantile SMA pattern is interpreted within clinical and molecular context.
- Specific SMN1 analysis addresses disease identity more directly than fiber shape alone.

Clinical expression reflects the extent and timing of neuron loss

- The disease causes progressive weakness through lower motor neuron depletion.
- Earlier and more severe neuronal involvement is associated with more severe phenotype.
- Later-onset forms typically evolve more gradually description.
- The supplied source does not establish a single predicted course for every treated patient.

5q-SMA forms vary in age of onset and clinical trajectory

Earlier onset



Type I / Werdnig-Hoffmann

First year of life; Most severe common form

Later onset



Other 5q-SMA variants

More gradual course

Childhood-adolescence



Type III / Kugelberg-Welander

Motor disability emerges later

SMA type I: The severe infantile form

- The most common severe 5q-associated phenotype is termed SMA type I.
- The historical eponym Werdnig–Hoffmann disease refers to this phenotype.
- Onset occurs during the first year of life description.
- Its severity is consistent with early and extensive loss of lower motor neuron input.

Type I survival figures are historical textbook descriptions

- Untreated or historical severe type I disease as usually fatal by age 2.
- The same source discusses gene and splice-modifying treatments that change therapeutic possibilities.
- Do not automatically apply historical natural-history outcomes to an individual receiving modern treatment.
- This lecture supplies no contemporary treatment-stratified survival estimates.

Later-onset SMA forms constitute a clinical spectrum

- The same SMN1-related disease mechanism can present later in childhood.
- Later-onset forms as having a more gradual course.
- The rate and timing of disability are important phenotypic distinctions.
- Copy-number-dependent residual SMN provides a molecular explanation for much of this variation.

SMA type III: Kugelberg–Welander phenotype

- SMA type III is identified as the Kugelberg–Welander disease phenotype.
- Motor disability usually becomes apparent during later childhood or adolescence.
- Its course is described as more gradual than severe infantile disease.
- The source does not assign an exact SMN2 copy count to this clinical label.

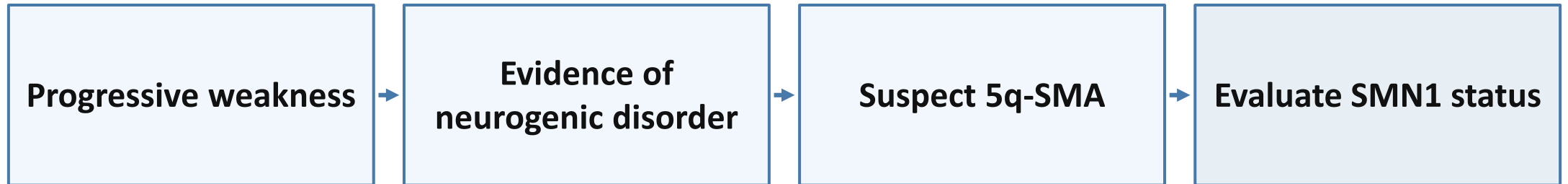
Clinical phenotypes explicitly

Phenotype	Onset	Course
SMA type I (Werdnig–Hoffmann)	First year of life	Severe; historically usually fatal by age 2
Other later-onset 5q-SMA	Later than severe infantile form	More gradual progression
SMA type III (Kugelberg–Welander)	Later childhood/adolescence	Motor disability usually develops later

Phenotype must not be inferred from the gene name alone

- SMN1 loss-of-function explains the common molecular origin.
- SMN2 dosage affects residual SMN and contributes to clinical variation.
- Timing of disease and observable motor function are separate clinical dimensions.
- Treatment can complicate comparison with historical untreated categories.

A pathology-based diagnostic reasoning sequence



SMN2 copy number then helps interpret phenotypic variability rather than replacing assessment of SMN1.

Conceptual reasoning aid, not a substituted clinical practice guideline.

Molecular assessment: Distinguish detection from modification

- SMN1 loss-of-function is the etiologic finding described for 5q-SMA.
- SMN2 copy-number variation supplies modifier information.
- A plausible molecular workflow separates causal SMN1 analysis from SMN2 dosage characterization.
- The provided Robbins excerpt does not specify assay platform, sensitivity, or official testing algorithm.

Causative, modifying, and morphologic evidence

Genetic evidence

- SMN1 loss-of-function: Explanatory disease lesion.
- SMN2 copy number: Phenotype modifier.
- Gene identity and gene dosage should be reported distinctly.

Pathologic evidence

- Lower motor neuron loss: Primary target.
- Neurogenic muscle atrophy: Downstream manifestation.
- Hypertrophied survivors: Compensatory adaptation.

Distinguishing adjacent motor neuron diseases

Feature	5q spinal muscular atrophy	Kennedy disease
Genetics	Autosomal recessive; SMN1 loss	X-linked; androgen receptor CAG expansion
Mechanism	Reduced SMN protein	Polyglutamine-repeat disease
Clinical emphasis	Childhood weakness; severity spectrum	Distal amyotrophy and bulbar signs
Additional features	SMN2 modifies phenotype	Androgen insensitivity and endocrine signs

How SMA differs from classic ALS framing

5q-SMA

- Genetically linked childhood forms.
- Lower motor neuron loss is the defining lesion here.
- SMN1/SMN2 system anchors the etiology.

ALS

- Often combines upper and lower motor neuron involvement.
- Has sporadic and multiple genetic forms.
- Not characterized by the 5q SMN1/SMN2 mechanism.

A neurogenic biopsy alone cannot classify the disorder

- Radiculopathy, peripheral neuropathy, ALS, and SMA can show neurogenic atrophy.
- The same downstream morphology can arise from lesions at different positions in the motor pathway.
- Anatomic and genetic context therefore change interpretation of similar muscle findings.
- Biopsy morphology is one level of evidence within a broader clinicopathologic assessment.

Mechanism-based therapy: Two approaches

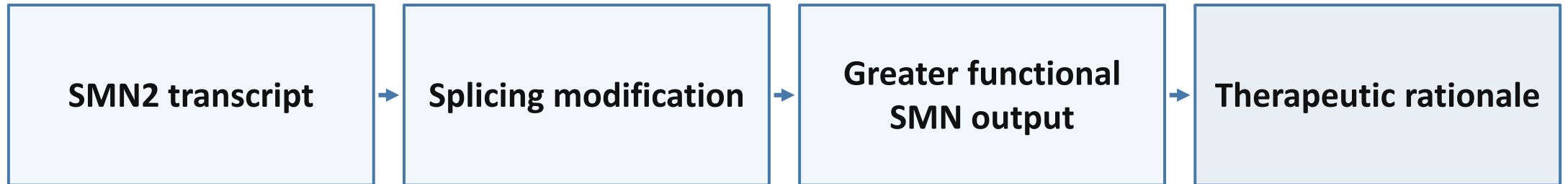
- Both described strategies aim to increase availability of functional SMN.
- One introduces a working SMN expression source with an adeno-associated viral vector.
- The other modifies splicing of SMN2-derived transcripts.
- These approaches intervene at different steps of the same causal chain.

Gene delivery targets the deficient protein source



A gene-delivery strategy; This is a mechanism diagram, not an efficacy or safety claim.

SMN2 splicing modulation uses the backup gene



Approved genetic therapies that alter processing of SMN2-derived RNA.

Compare the two therapeutic mechanisms

SMN expression delivery

- Introduces a source of functional SMN expression.
- Uses an adeno-associated viral delivery system.
- Targets the deficit after SMN1 loss.

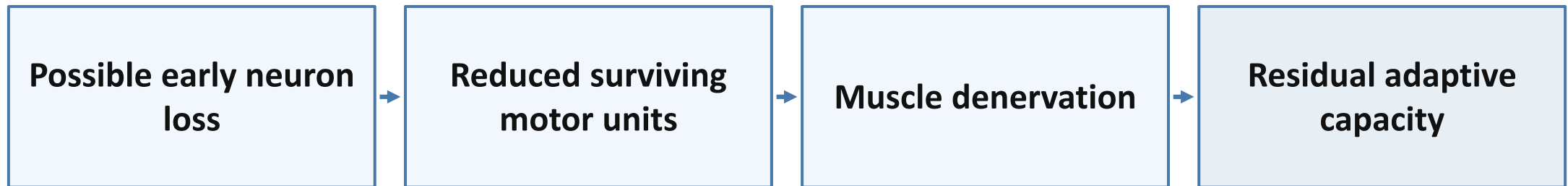
SMN2 transcript modulation

- Acts on RNA processing rather than SMN1 DNA.
- Exploits the adjacent SMN2 gene.
- Aims to alter the ratio of productive transcript output.

What cannot be concluded from the treatment paragraph

- The textbook paragraph does not provide trial effect sizes or long-term comparative outcomes.
- It does not establish a patient-specific sequence of therapies or dosing regimen.
- Its quoted acquisition cost is time- and setting-dependent and is not a biologic property.
- Mechanistic understanding should be separated from current regulatory and clinical guidance.

Why timing of therapeutic SMN restoration may matter



The source notes neuronal loss may begin in utero; A mechanistic inference is that replacing SMN cannot simply resurrect neurons already lost.

Interpretive teaching inference, not an efficacy threshold.

Case exercise: Severe early motor disorder

A child develops progressive motor weakness during the first year of life. A muscle sample, if examined, is described as showing many markedly small rounded fibers with scattered large survivors.

Which upstream lesion and muscle mechanism connect these observations?

Case interpretation: Severe infantile pattern

- An SMN1 loss-of-function genotype is the causal molecular model of common 5q-SMA.
- Marked lower motor neuron loss can start in utero or early after birth.
- Absent innervation produces the small rounded myofiber population.
- Rare normal or enlarged fibers can be explained by surviving innervation.

Case exercise: Later childhood weakness

A patient begins to develop motor disability in later childhood. Molecular analysis identifies a disease-associated SMN1 loss-of-function genotype.

How can this be reconciled with a less severe course than infantile SMA?

Case interpretation: Variable phenotypic severity

- The common causal molecular defect can be shared across distinct 5q-SMA phenotypes.
- SMN2 copy number influences residual functional SMN protein.
- Later onset and a more gradual course are consistent with the textbook description of type III.
- A precise prognosis or copy-number threshold cannot be asserted from this vignette alone.

Case exercise: Neurogenic pathology

A muscle sample shows clusters of similarly typed fibers and regions of atrophy. No genetic data are supplied.

What can morphology establish—and what remains unresolved?

Case interpretation: Morphology is not etiology

- Fiber-type grouping is consistent with collateral reinnervation following denervation.
- Grouped atrophy can follow failure of an enlarged reinnervated motor unit.
- Several disorders of the motor unit can produce these findings.
- A neurogenic pattern alone cannot identify SMN1 loss-of-function.

High-yield integration: Gene → neuron → myofiber

- SMN1 loss-of-function decreases the principal source of survival motor neuron protein.
- SMN2 splicing and copy number influence residual functional SMN availability.
- Lower motor neuron loss results in denervation and progressive muscle weakness.
- Severe infantile muscle demonstrates extensive rounded atrophy and rare enlarged surviving fibers.

Six interpretive pitfalls to avoid

Common mistake	Correction
SMA is a primary myopathy	Primary lesion is lower motor neuron loss
SMN2 causes all 5q-SMA	SMN1 loss is causal; SMN2 is a modifier
Every atrophic fiber is angular	Infantile SMA can show rounded atrophic fibers
Large fibers exclude denervation	Surviving innervation can produce hypertrophy
Biopsy proves SMN1 etiology	Neurogenic morphology is not gene-specific
Historical outcomes equal treated prognosis	Therapies modify the natural-history context

Primary reference and source boundaries

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026)

Chapter 28 — Spinal Muscular Atrophy; motor neuron disease context.

Chapter 27 — Neurogenic muscle atrophy and SMA muscle morphology.

For muscle microanatomy, refer to the original textbook description and Figure 27.8; diagrams shown here are explicitly schematic.